Quantitative Magnetic Resonance Imaging of Human Brain Development: Ages 4–18

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Brain magnetic resonance images (MRI) of 104 healthy children and adolescents, aged 4–18, showed significant effects of age and gender on brain morphometry. Males had larger cerebral (9%) and cerebellar (8%) volumes ($P < 0.0001$ and $P = 0.008$, respectively), which remained significant even after correction for height and weight. After adjusting for cerebral size, the putamen and globus pallidus remained larger in males, while relative caudate size was larger in females. Neither cerebral nor cerebellar volume changed significantly across this age range. Lateral ventricular volume increased significantly in males (trend for females), with males showing an increase in slope after age 11. In males only, caudate and putamen decreased with age ($P = 0.007$ and 0.05, respectively). The left lateral ventricles and putamen were significantly greater than the right ($P = 0.01$ and 0.0001, respectively). In contrast, the cerebral hemispheres and caudate showed a highly consistent right-greater-than-left asymmetry ($P < 0.0001$ for both). All volumes demonstrated a high degree of variability. These findings highlight gender-specific maturational changes of the developing brain and the need for large gender-matched samples in pediatric neuropsychiatric studies.

Introduction

Surprisingly little is known about human anatomical brain development between the ages 4 and 18. Mortality is low, with accidents the leading cause of death, and autopsies are rarely performed. This point is exemplified by the Yakovlev brain collection in Washington, DC, in which only 12 of the 483 normal brains from the second embryonic week to the tenth decade of life are from subjects aged 4–18 years (Haleem, 1990).

Although by age 2 the brain has reached 75% of its adult weight (Carmichael, 1990) and the processes of synaptic pruning and cell death are most active during these early years, changes in brain structure and physiology continue throughout life (Huttenlocher, 1979; Huttenlocher *et al.*, 1982; Easter *et al.*, 1985; Kretschmann *et al.*, 1986; Chugani *et al.*, 1987). For example, the associative neocortex continues to develop well into the third decade (Yakovlev and Lecours, 1967), as does the corpus callosum, which connects all major subdivisions of the cerebrum (Pujol *et al.*, 1993).

Magnetic resonance imaging (MRI), with its lack of ionizing radiation and excellent anatomical resolution, provides an unprecedented opportunity to obtain *in vivo* neuroanatomical information of children and adolescents. To date, however, few studies have been carried out for this group. One study of 39 subjects aged 8–35 (Jernigan *et al.*, 1991) found an apparent linear age-related decrease in cortical (frontal and parietal regions) and subcortical structures (gray matter nuclei) and an increase in ventricular volume across this age range. A second study of 88 clinically referred subjects aged 3 months–30 years found a steady increase in cortical white matter until the age of 20, with cortical gray matter volume peaking at age 4 and then decreasing. Cortical and ventricular cerebrospinal fluid (CSF) volumes remained constant (Pfferbaum *et al.*, 1994). An increase in intracranial volume of ~300 ml was seen between 3 months and 10 years, with most of this increase occurring by the age of 5. Finally, an MRI study of dyslexia that included 14 non-impaired children, aged 7–9, noted larger brain sizes in male subjects and age-related increases in brain structure sizes (Schultz *et al.*, 1994).

These studies provide important information about key aspects of developmental neuroanatomy. Clearly, there are substantial brain maturational changes in these years that may reflect or predict normal behavioral development. However, most childhood neuropsychiatric disorders are diagnosed and followed between the ages of 4 and 18–an age range underrepresented in these previous studies. Large data sets of well-defined normal subjects are still needed to obtain accurate quantification of the highly variable developmental changes of children and adolescents.

This need is particularly relevant for ongoing MRI studies addressing hypothesized subtle deviations in brain development in children with severe neuropsychiatric disorders. Several gross anatomic structures have already been implicated in a variety of childhood-onset disorders including basal ganglia anomalies in attention-deficit/hyperactivity disorder (ADHD) (Hynd *et al.*, 1993; Castellanos *et al.*, 1994), Sydenham's chorea (Giedd *et al.*, 1995b) and Tourette's syndrome (Peterson *et al.*, 1993; Singer *et al.*, 1993); midsagittal corpus callosum area differences in dyslexia (Hynd *et al.*, 1990, 1995; Duara *et al.*, 1991) and ADHD (Hynd *et al.*, 1990, 1991; Giedd *et al.*, 1994; Semrud-Clikeman *et al.*, 1994); and cerebral volume, planum temporale and asymmetry differences in dyslexia and other learning disorders (Galaburda *et al.*, 1985; Rumsey *et al.*, 1986; Duara *et al.*, 1991; Larsen *et al.*, 1991; Galaburda, 1993; Kushch *et al.*, 1993). Interpretation of these studies has been limited by the small sample sizes and lack of normative data.

To address this lack, and to assess normal brain maturational changes, a large group of medically and psychiatrically healthy children and adolescents were recruited from the local community for participation in a quantitative MRI study. The common practice of using as controls children referred clinically for MRI and whose scans were subsequently read as normal was avoided because children referred for clinical scans are overrepresented in diagnostic groups, such as ADHD. Conversely, some clinically normal children may have scans read by radiologists as 'abnormal' and excluding these subjects would confound statistical comparisons with diagnostic groups.

This initial report is the first of a series examining the relationship between age, gender and brain morphometry in a sample of >100 healthy children and adolescents. Based on earlier studies, we anticipated that a number of late maturational changes would be seen, such as decreases in subcortical nuclei volumes and increases in ventricular volumes (Jernigan *et al.*,

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1991; Pfefferbaum *et al.*, 1994). We hoped that with our larger sample size and more accurate methodology, effects of gender and laterality could also be addressed.

Materials and Methods

Subjects

From 624 responses to our local newspaper advertisements and postings, 234 were excluded by telephone screening due to personal or familial histories of learning disorders, ADHD or ongoing medical or psychiatric disorders. The remaining 390 were sent packets containing the Child Behavior Checklist (Achenbach and Edelbrock, 1983), an NIH medical history form and Conners' 48-item Parent Questionnaire (Werry *et al.*, 1975; Goyette *et al.*, 1978). Conners' 39-item Teacher Questionnaires were sent directly to the children's teachers. Based on this information, 187 children were excluded due to histories of learning disorders, behavioral problems at home or school, or medical problems such as head injury, migraines or use of medication. The remaining 203 were brought into the clinic for a physical and neurological examination; the 12 handedness items from the Physical and Neurological Examination for Subtle Signs (PANESS) inventory (Denckla, 1985); a clinical psychiatric interview of the parents and child using the Child and Parent Diagnostic Interview for Children (Welner *et al.*, 1987); a clinical interview of parent and child by a board-certified child psychiatrist (J.N.G.) including family history assessment; Vocabulary, Block Design, and Digit Span subtests of the Wechsler Intelligence Scale for Children–Revised (WISC-R) (Wechsler, 1974) for subjects 6–16 years of age or the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (Wechsler, 1981) for subjects aged 16 or older; spelling subtest of the Wide Range Achievement Test–Revised (Jastak and Wilkinson, 1984); and reading achievement cluster (consisting of letter-word identification, word attack, and passage comprehension) of the Woodcock-Johnson Psycho-educational Battery (Woodcock and Johnson, 1977). Individuals with physical, neurological or lifetime histories of psychiatric abnormalities or learning disabilities, or who had first-degree relatives or >20% of second-degree relatives with major psychiatric disorders were excluded. Older siblings were removed from the data set to maintain independence between subjects. One hundred and twelve subjects met all of the above criteria and returned for the scanning procedure. Four children (ages 5, 7, 8 and 11) who had been accepted for the study were unable to complete the scan due to claustrophobia or anxiety, and four scans had excessive motion artifact, which prevented accurate measurement.

Fifty-five male and 49 female subjects (mean age = 11.6 years, SD = 3.5, range 4.7–17.8 years) were included in this analysis. There were significant male greater than female group differences for height ($t = 2.37$, $P = 0.02$) and Vocabulary subtest score of the WISC-R ($t = 1.99$, $P = 0.05$), and a trend for weight ($t = 1.90$, $P = 0.06$). There were no significant group differences on age, handedness, Tanner stage, total academic score on the Woodcock-Johnson test, or Digit Span and Block Design subtests of the WISC-R. Subject characteristics are shown in Table 1. As can be seen, the subjects were above average on Vocabulary, Block Design and Digit Span subtests. Our strict inclusion criteria make this outcome likely, although it does limit the generalizability of these findings.

The protocol was approved by the Institutional Review Board of the National Institute of Mental Health. Written consent from the parents and assent from the children were obtained.

MRI Acquisition

All subjects were scanned on the same GE 1.5 tesla Signa scanner. Three T_1-weighted three-dimensional image sets, with slice thickness of 1.5 mm in the axial and sagittal planes and 2.0 mm in the coronal plane were obtained using three-dimensional spoiled gradient recalled echo in the steady state (3D SPGR). Imaging parameters were as follows: time to echo, 5 ms; repetition time, 24 ms; flip angle, 45°; acquisition matrix, 192 × 256; number of excitations, 1; field of view, 24 cm. Vitamin E capsules, wrapped in gauze and placed in the meatus of each ear, were used to help standardize head placement. A third capsule was taped to the lateral aspect of the left inferior orbital ridge. The vitamin E capsules are readily identifiable on the scans and were used to define a reference plane for our images. The patient's head was aligned in a head holder so that a narrow guide light passed through each of the vitamin E capsules. Foam padding was placed on both sides of the patient's head to minimize head movement. A sagittal localizing plane was acquired and from this a multi-echo axial series to ensure that one of the axial slices contained all three of the capsules. If no slice clearly contained all three capsules, the patient was realigned until this criterion was met. Alignment in the remaining plane was standardized by having the subject's nose at the '12:00' position. Subjects were scanned in the evening to promote their falling asleep in the scanner. Younger children were allowed to bring blankets or stuffed animals into the scanner and have their parents read to them. No sedation was used.

Table 1
Characteristics of healthy MRI subjects, ages 4–18

	Male	Female
Sample size	55	49
Age (years)	12.1 (3.1)	11.0 (3.8)
Height (cm)	154.4 (19.6)	145.0 (20.8)*
Weight (kg)	46.6 (16.4)	40.5 (15.9)
Tanner stage	2.4 (1.6)	2.2 (1.5)
Handedness	90% right-handed	90% right-handed
Vocabulary[a]	13.8 (2.9)	12.7 (2.5)*
Block design[a]	13.4 (2.7)	12.7 (3.5)
Digit span[a]	11.2 (2.3)	11.4 (2.5)
Woodcock–Johnson	516 (33)	494 (71)

[a]Subtests of the Wechsler Intelligence Scale for Children—Revised.

*$P < 0.05$ difference between genders.

Image Analysis

Clinical Interpretation

All scans were evaluated by a clinical neuroradiologist. Two subjects were found to have clinically insignificant increased T_2 signal intensities: one in the area of the left semiovale and the other in the right parietal lobe. They were retained in the data set. No other gross abnormalities were reported.

Cerebrum and Cerebellar Quantification

A novel image analysis technique developed by one of the authors (J.W.S.) was employed to separate the image of the brain from the surrounding intracranial cavity and to quantify cerebrum and cerebellar volumes. This technique used an active surface template of a brain to supplement the sometimes ambiguous MR imaging characteristics. The elastically deformable model of the brain surface was conformed to the features of the input image through successive iterations of an energy minimization function (Fig. 1, top and bottom). The resulting image was then hand edited by experienced raters examining each axial slice and removing artifacts related to patches of eyeball or dura. Intraclass correlations for the volumes of the edited brains were 0.99 for interrater reliability and 0.92 by comparison to volumes derived from more conventional slice-by-slice hand tracing through all axial slices on which brain matter is visible. The technique can be qualitatively evaluated by comparison with a post-mortem specimen (Fig. 2). Further details are provided elsewhere (Snell *et al.*, 1995).

Spatial orientation was standardized by rotating the brains in three dimensions so that operator-selected midline anterior and posterior commissure points were in the same axial plane and that this plane was perpendicular to an operator-selected midsagittal plane. Once each brain's spatial orientation was standardized, the left and right cerebral hemispheres were further subdivided into five regions based on internal landmarks. The boundaries for the regional brain volumes are shown in Figure 3.

Region I ('prefrontal' sector) consists of all brain matter in front of the anteriormost point of the corpus callosum. Region II ('premotor/temporal' sector) is bounded by the coronal plane intersecting the anteriormost point of the corpus callosum and the coronal plane intersecting the anterior commissure (AC). Region III ('precentral/

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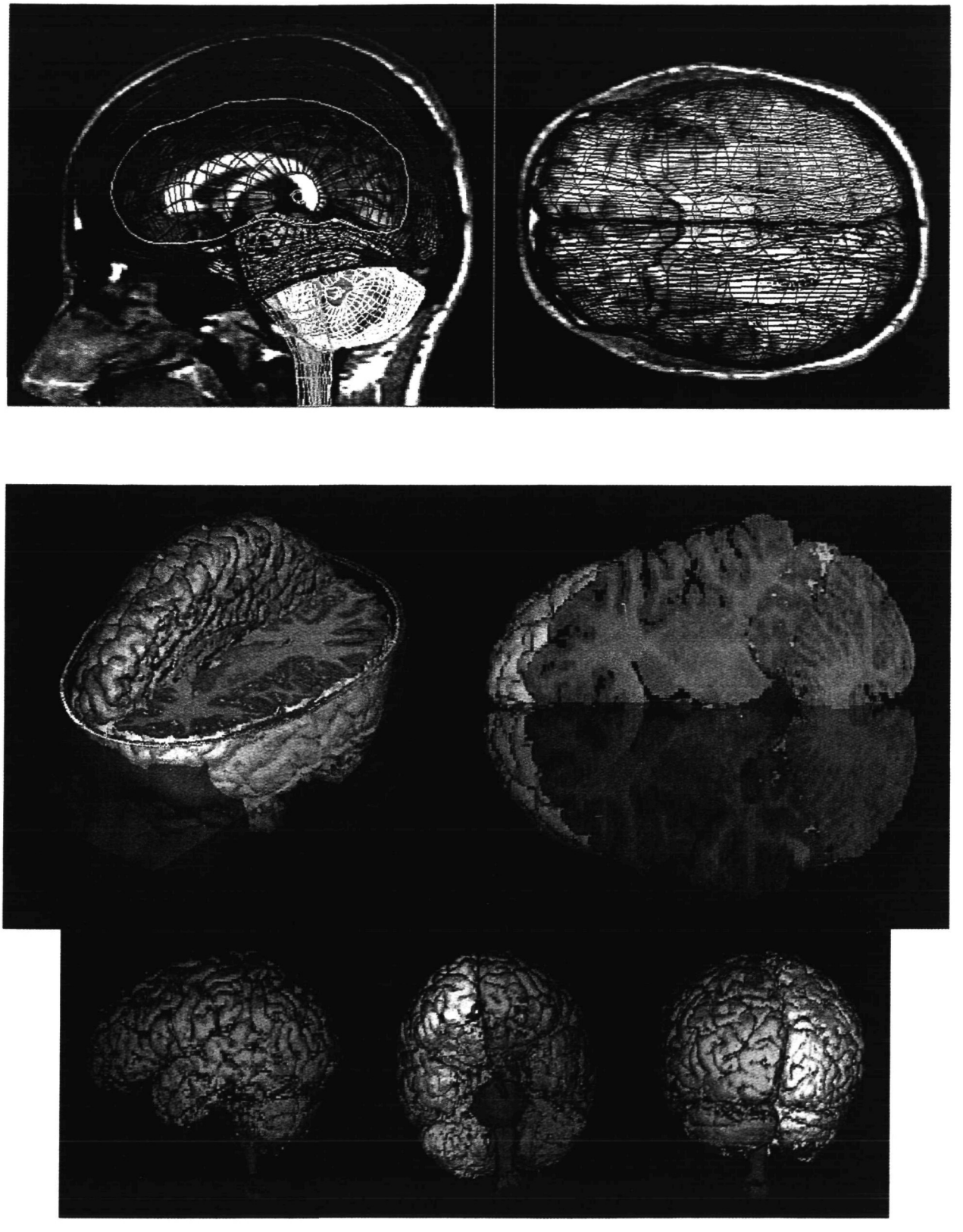

Figure 1. (*Top*) The brain active surface template deforms in response to the image data set such that the model surfaces are brought into correspondence with the brain. Curvature and topology constraints are used to overcome low-contrast boundary ambiguities. (*Bottom*) The final surface configuration of the active surface template is used to segment and quantify the left and right cerebrum and cerebellum.

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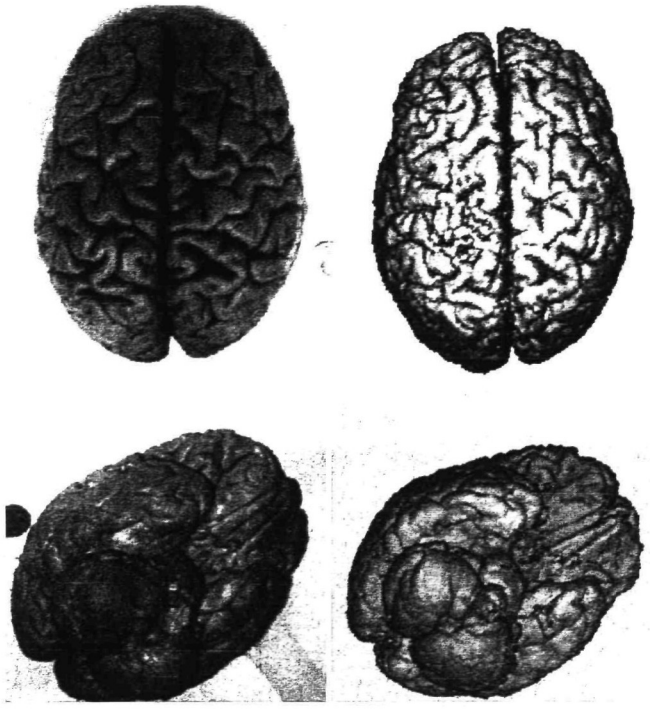

Figure 2. The active surface template method was validated by comparison with post-mortem specimens. The brain was segmented from three-dimensional MRI of whole cadaver heads (*above right*) and compared visually and volumetrically with manual dissection results (*above left*).

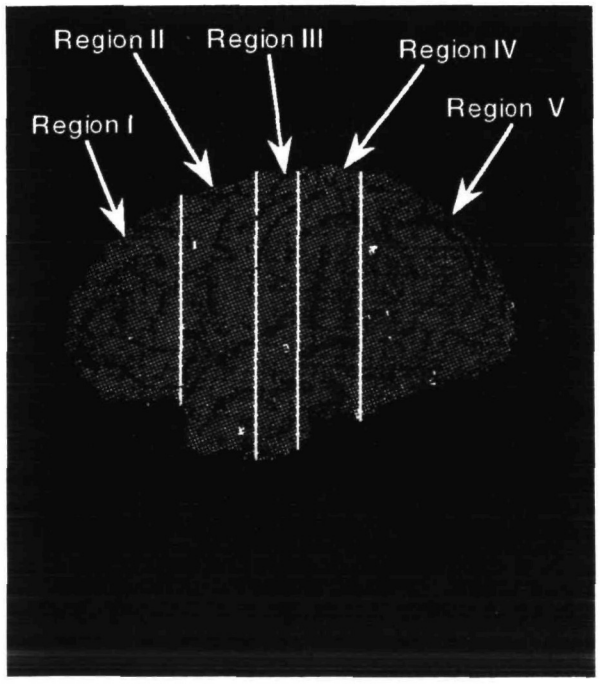

Figure 3. Boundaries for cerebral subdivisions are defined by coronal planes intersecting internal landmarks. Planes intersecting the anteriormost point of the genu of the corpus callosum, the anterior commissure (AC) and the posterior commissure (PC) were used to demarcate regions I, II and III (prefrontal, premotor/temporal and precentral/temporal). Region IV (parietal/temporal) and region V (occipital) are arbitrarily divided by a plane 1.5 times the AC–PC length posterior to the PC.

temporal' sector) is between the anterior and posterior commissures (PC). The two posterior regions—region IV ('parietal/temporal' sector) and region V ('occipital' sector)—are arbitrarily divided by a plane 1.5 times the AC–PC length posterior to the PC. The descriptive names are in quotations to emphasize that they are used only for the sake of communication and are not based on sulcal/gyral patterns or cytoarchitectonic information, and thus should be interpreted only as containing 'mostly' prefrontal tissue, or 'mostly' premotor and temporal tissue, and so on.

Lateral Ventricle Quantification

Lateral ventricular volumes were measured in the coronal plane on all slices in which they were visible using an operator-supervised thresholding technique, which segmented cerebrospinal fluid from brain tissue (Rasband, 1993). Because this process required little subjectivity, interrater reliability was extremely high (ICC > 0.99).

Subcortical Gray Matter Quantification

The caudate and putamen were manually outlined from coronal slices on a Macintosh IIfx workstation using NIH Image software (Rasband, 1993). Since the sum of areas from the odd-numbered slices for the first 20 subjects correlated highly with the sum of the areas from the even-numbered slices (ICC = 0.98), subsequent outlining was done on every other slice and then multiplied by a slice thickness of 4 mm to derive volume. Interrater reliability (ICC = 0.88 and 0.84 for the caudate and putamen, respectively) was assessed initially and periodically during the analyses to monitor potential 'drifts' in operator measurements. Manual outlining of basal ganglia structures by experienced raters was judged to be superior to a variety of automated techniques examined by our group.

Table 2
ANOVA and ANCOVA (adjusting for total cerebral volume) for brain structures by gender and side in healthy children and adolescents, aged 4–18 (n = 104)

	ANOVA		ANCOVA		
	F value	*P* value	*F* value	*P* value	Comment
Cerebrum					
Gender	19.8	0.0001			M > F
Side	38.3	0.0001			R > L
Ventricles		NS		NS	
Gender					
Side	6.5	0.01	5.7	0.02	L > R
Cerebellum	5.4	0.02		NS	M > F
Gender					
Side		NS		NS	
Caudate		NS	6.5	0.01	F > M
Gender					
Side	58.6	0.0001	57.3	0.0001	R > L
Putamen	16.9	0.0001	7.8	0.006	M > F
Gender					
Side	97.5	0.0001	97.5	0.0001	L > R
Globus pallidus	11.9	0.0008	9.1	0.003	M > F
Gender					
Side		NS		NS	
Region I	5.3	0.02		NS	M > F
Gender					
Side	4.8	0.03	4.6	0.03	R > L
Region II	7.1	0.009		NS	M > F
Gender					
Side	3.2	0.08	3.1	0.08	R > L
Region III	1.9	0.10		NS	M > F
Gender					
Side		NS		NS	
Region IV	3.1	0.08		NS	M > F
Gender					
Side		NS		NS	
Region V	1.9	0.18		NS	M > F
Gender					
Side			NS		NS

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The globus pallidus, bounded medially by the internal capsule and laterally by the putamen, was also measured on coronal sections, but included every slice, beginning 2 mm anterior to the anterior commissure and proceeding posteriorly for a total of 14 mm. Limiting sampling to this domain, which encompassed almost the entire globus pallidus in the majority of subjects, was necessary to achieve adequate interrater reliability (ICC = 0.82).

Because volumetric quantification of the thalamus was beyond our current methodology, the thalamic area was outlined using a supervised thresholding technique (Rasband, 1993) from a single midsagittal slice reconstructed from the axial series. Reslicing from the axial series allows more precise designation of the midsagittal plane than choosing a 'best' midsagittal slice from the sagittal series. The intraclass correlation coefficient of interrater reliability for the thalamic area was 0.85.

Statistical Analysis

The SAS general linear model procedure was used to examine the relationship between age, gender and brain morphology (SAS Institute, 1990). This included linear regression models for total group and gender-specific effects of age on brain structure volumes. Since total cerebral volume differed significantly between genders, gender differences were analyzed using ANOVA and then ANCOVA to adjust for total cerebral volume.

In addition, linearity and constant variance assumptions were relaxed by use of a local regression procedure that retained the subtle non-linearities in the data (a 'super-smoother'; see Hastie and Tibshirani, 1990) to yield smooth, curvilinear and gender-specific adaptive fits to the scatterplots of structure volumes by age.

Combining male and female data in a single classical statistical model usually makes linear and equal variance assumptions that were not always supported by our data and could, in some cases, have yielded artifactual results. We employed the local regression procedure as a descriptive graphical tool and, for statistical inference, fitted classical linear and piecewise linear regression models separately by gender. We have, however, included results from combined analyses (Table 3) to enable comparison of our results with previous reports.

Results

Results are summarized in Tables 2 and 3 and Figures 3 and 4. A striking feature, evident from the scatterplots, is the high degree of variability in brain structure size even for our well-screened, healthy population. Consistent with a previous report, subcortical nuclei volumes decrease and ventricular volume increases (Jernigan *et al.*, 1991). Not previously reported for this age group, however, are the gender and laterality effects for both volumes and maturational changes.

Table 2 shows ANOVAs for gender and side (left or right) and ANCOVAs adjusting for total cerebral volume. Table 3 shows the linear regression slopes with age, by gender and side, for the various structures.

Total (left plus right) volumes are presented as scatterplots, with respect to gender and age, in Figures 4 and 5. Curvilinear summaries for each gender are superimposed. Linear summaries appear in the upper right portion of each plot. Notable maturational changes are the increases in total ventricular volume and decreases in caudate and putamen volumes, which are significant only for males.

Gender

Robust gender effects were seen for several measures. Male cerebral volumes were larger than female by 8.7% ($F = 19.8$, $P < 0.0001$). This effect remained after correction for height and weight ($F = 16.5$, $P < 0.0001$), and was a fairly uniform difference in that none of the cerebral subdivisions showed sexual dimorphism when corrected for total cerebral volume. The cerebellum was also larger (8.0%) in males ($F = 5.4$, $P = 0.02$). For subcortical structures, the putamen and globus pallidus were larger in males ($F = 16.1$, $P = 0.001$ and $F = 8.0$, $P = 0.006$, respectively), and remained so after adjusting for total cerebral volume ($F = 6.3$, $P = 0.01$ and $F = 4.1$, $P = 0.05$). In contrast, caudate was larger in females after adjustment for total cerebral volume ($F = 6.5$, $P = 0.01$). The unadjusted volumes of the caudate, lateral ventricles and thalamic area did not differ between genders.

Age-Related Change

Neither right, left, nor total cerebral or cerebellar volume increased significantly with age for either gender. The regional subdivisions of the cerebrum also did not show significant age effects. Lateral ventricular volume increased with age (slope = 0.88 ml/year, $P = 0.0007$ and slope = 0.47 ml/year, $P = 0.06$ for males and females, respectively). Interestingly, the increase for males occurred almost entirely after the age of 11. A piecewise linear model for males revealed a significant change in slope after the age of 11 ($P = 0.03$) not shared by females at that or other ages. Both caudate and putamen volume decreased in males (slope = -0.01 ml/year, $P = 0.007$ and slope = -0.007 ml/year, $P = 0.05$, respectively), but not in females. Neither globus pallidus

Table 3

Linear regression of brain structures with age by gender and side in healthy children and adolescents ($n = 104$)

	Right						Left					
	Male		Female		Total		Male		Female		Total	
	Slope	*P*	Slope	P	Slope	P	Slope	*p*	Slope	*P*	Slope	*P*
Cerebrum	–0.15	0.46	0.23	0.18	0.17	0.25	–0.12	0.57	0.26	0.11	0.20	0.18
Ventricles	0.04	0.0003	0.02	0.09	0.03	0.0002	0.04	0.004	0.02	0.06	0.03	0.0004
Cerebellum	0.02	0.73	0.05	0.25	0.05	0.19	–0.02	0.74	0.06	0.21	0.04	0.31
Caudate	–0.005	0.01	0.0006	0.82	–0.002	0.22	–0.005	0.006	0.0005	0.81	–0.002	0.16
Putamen	–0.003	0.06	–0.002	0.28	–0.002	0.22	–0.003	0.07	–0.002	0.18	–0.002	0.15
Globus pallidus	0.0002	0.82	–0.0007	0.22	–0.0001	0.90	0.0001	0.94	–0.0004	0.49	–0.00004	0.93
Thalamus[a]	–0.25	0.07	0.10	0.44	–0.06	0.51			Unilateral measurement[a]			
Region I	–0.06	0.20	0.001	0.97	–0.01	0.75	–0.06	0.29	0.04	0.38	0.004	0.90
Region II	–0.01	0.88	0.006	0.93	0.01	0.80	–0.007	0.94	0.04	0.51	0.03	0.54
Region III	0.14	0.22	0.05	0.60	0.10	0.16	0.15	0.18	0.06	0.54	0.11	0.12
Region IV	0.14	0.29	0.05	0.66	0.11	0.20	0.16	0.23	0.04	0.70	0.12	0.17
Region V	–0.31	0.22	0.13	0.50	–0.03	0.83	–0.32	0.19	0.08	0.70	–0.06	0.72

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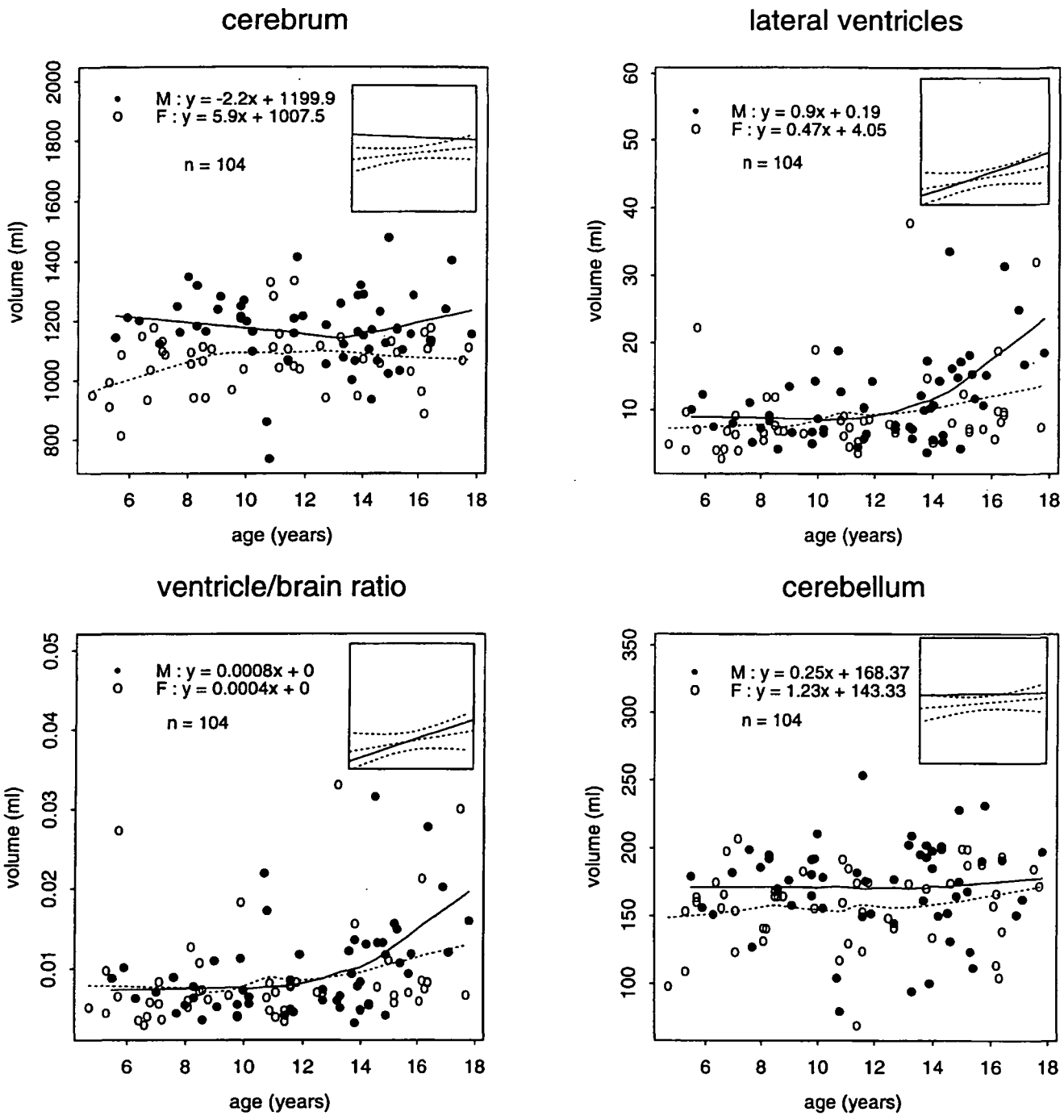

Figure 4. Scatterplots by age and gender of total cerebral volume, ventricular volume, ventricle:brain ratio and cerebellar volume for children and adolescents (n = 104).

volume nor thalamic area changed significantly with age for either gender.

Asymmetries

Several right/left asymmetries were highly significant (Table 2). Right cerebral hemisphere and caudate volumes were larger than left (F = 38.3, P < 0.0001 and F = 58.6, P < 0.0001, respectively), whereas left lateral ventricles and putamen were larger than the right (F = 6.5, P = 0.01 and F = 97.5, P < 0.0001, respectively). There were no significant differences between genders for these asymmetries. No asymmetry was seen for the cerebellar hemispheres. Consistent with reports from the adult literature (Bilder *et al.*, 1994), the anteriormost subdivision of the cerebrum demonstrated a right-greater-than-left asymmetry (F = 4.8, P = 0.03).

Ventricle:Brain Ratio

A ventricle:brain ratio, calculated from the lateral ventricle and

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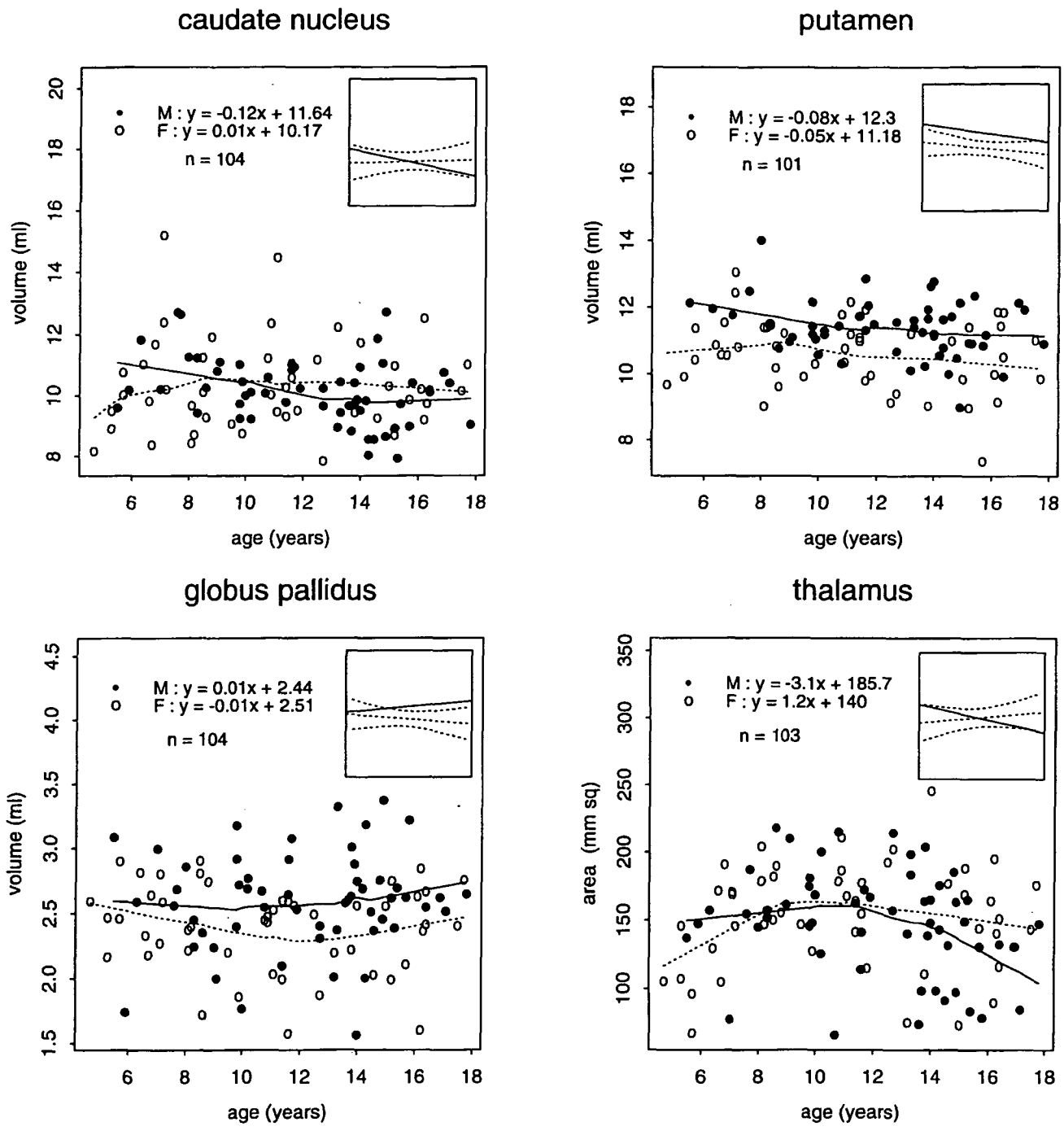

Figure 5. Scatterplots by age and gender of subcortical gray matter volumes (right + left) for children and adolescents (n = 104).

cerebral hemisphere measures, was nearly collinear with lateral ventricular volume (Fig. 4) and did little to reduce variance of the ventricular measures. It is presented for comparison with the wide body of literature related to this measure.

Discussion

A number of findings emerge from these data confirming and extending previous reports for pediatric subjects. As expected, there are age-related decreases in caudate and putamen and increase in ventricular volume. As reported for adult samples (Breier *et al.*, 1992; Flaum *et al.*, 1995), there is a highly significant right-greater-than-left asymmetry of the caudate. In addition, gender-specific maturational effects were noted for these volumes.

The larger sample size in this study permitted closer examination of sexual dimorphism than possible in earlier reports. For instance, a previous study of 23 males and 16 females, aged 8–35, showed a decrease with age for the caudate and lenticular nucleus, but no effect for gender (Jernigan *et al.*, 1991). The present study demonstrated similar declines in

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caudate and lenticular volume (derived by summing putamen and globus pallidus for this comparison), but only for males. More global gender effects, e.g., larger male brains with no regional differences when adjusting for total brain volume, are also consistent with previous reports (Jernigan *et al.*, 1991; Pfefferbaum *et al.*, 1994).

Sexual dimorphism of brain structures may be related to the X chromosome, hormonal effects, environmental effects or a combination of these. A recent study of Turner's syndrome (Murphy *et al.*, 1993) suggested that the X chromosome is involved in determining the adult size of the caudate, lentiform nucleus, thalamus and gray matter of the cerebral cortex. Hormonal effects seem to be instrumental in overall brain size and cerebral asymmetries (Kelley, 1993).

The larger size of the male brain in this age group parallels both autopsy (Blinkov and Glezer, 1968; Ho *et al.*, 1980) and imaging studies (Andreasen *et al.*, 1993; Filipek *et al.*, 1994; Pfefferbaum *et al.*, 1994; Schultz *et al.*, 1994). Although there are several smaller structures that are thought to be sexually dimorphic (anterior commissure, corpus callosum, and certain thalamic nuclei), at a macroscopic level the larger size of the male cerebrum appears relatively uniform, as none of the regional subdivisions showed sexual dimorphism after correction for total cerebral volume. Of course, gross structural size may not be sensitive to sexually dimorphic differences in connectivity between different neurons, known differences in receptor density, or more subtle differences in the size or connectivity of various nuclei. Given the multiple parameters determining brain size, a larger size should not be interpreted as imparting functional advantage or disadvantage.

The lack of increase in total cerebral size across this age range is consistent with available post-mortem data and previous MRI studies (Jernigan *et al.*, 1991; Pfefferbaum *et al.*, 1994), indicating a leveling off in total brain size at ~5 years (Kretschmann *et al.*, 1986), although other investigators reported an ~100 cm^3 increase from ages 5 to 18 (Blinkov and Glezer, 1968). Head circumference increases by ~2.0 in. in boys and ~1.9 in. in girls from ages 5 to 18 (Nellhaus, 1968), which may be accounted for by the increase in ventricular volume and/or skull thickening that is known to occur across this age range (Shapiro and Janzen, 1960). The phenomenon of a progressively decreasing brain:body weight ratio during development is well described in the literature (Dekaban and Sadowsky, 1978), although a complete lack of increase in brain size during this developmental period is perhaps surprising.

While the age-related changes in the cerebellum, caudate and putamen are of interest, the interpretation of these changes is not clear. The size of brain structures is determined by the number, size and packing density of constituent cells, namely neurons and glial cells. Like the nervous systems of other higher vertebrates, human brain development takes place by an overproduction and then selective elimination of cells, with the number of neurons reaching its maximum *in utero* (Rabinowicz, 1986). The balance between cell proliferation and cell death during neurogenesis largely accounts for the total number of neurons. For a short time after birth, certain types of neurons, granule cells in the cerebellum, olfactory bulb, hippocampal dentate gyrus and brainstem nuclei may proliferate, but these account for a small fraction of the total number of neurons (Jacobson, 1991). Individual neurons undergo many cyclical changes in size throughout development (Thatcher, 1992), but in general enlarge with age (Blinkov and Glezer, 1968). As neighboring neurons are lost through apoptosis or cell death, the remaining neurons sprout greater numbers of dendrites, axons become thicker and the number of synaptic boutons increases. Axonal and dendritic changes continue throughout life and are presumably involved in the mechanisms by which we learn (Werry, 1991).

Glial cells outnumber neurons, with reports of glial cell:neuron ratios ranging from 1.7 to 10 (Brizzee *et al.*, 1964). Unlike neurons, glial cells undergo a constant cycle of proliferation and cell death. The relationship between glial cell volume and the size, number or activity of neurons is poorly understood, although both metabolic activity and neuronal cell death are thought to influence glial proliferation (Jacobson, 1991). Myelination by oligodendrocytes is the activity of glial cells most influential in determining brain size during this age range. Myelination continues actively at least through the first decade (Yakovlev and Lecours, 1967) and longer in certain parts of the brain, such as the superior medullary lamina along the surface of the parahippocampal gyrus, where there is a doubling in the extent of myelination relative to brain weight between the first and second decades, and an additional 60% increase between the fourth and sixth decades (Benes *et al.*, 1994).

The balance between decreasing numbers of neurons and increasing size of neurons and glial cells, largely attributable to myelination, is primarily responsible for determining the overall size of the brain and its components. Synaptic pruning alone, despite its ongoing activity during this age period, is less likely to be a major factor in overall structure size. Based on work involving the primary visual cortex of the macaque monkey (Bourgeois and Rakic, 1993), it is estimated that even a total loss of boutons would account for only a 1–2% decrease in volume. However, the effect synaptic pruning has on the remaining thickness of the parent axon or dendritic branches has yet to be determined. Another parameter in structure size is packing density, which is influenced by hydration, extracellular volume and degree of vascularity.

Neurons, glial cells and packing density are, in turn, affected by many factors, including genetics, hormones, growth factors and nutrients in the developing nervous system (Jacobson, 1991). In addition, diet and other external factors such as infections, toxins, trauma, stress or degree of enriched environment (Diamond *et al.*, 1964) may also have a role in determining structure size. The extent to and the mechanisms by which neuropsychiatric disorders affect these parameters must be part of future investigations.

The caudate and putamen, which decrease significantly in size with age for males only, and the striking ventricular enlargement found in males exemplify important gender-by-age differences. These sexually dimorphic effects are of great interest in normal development as they occur in regions implicated in various neuropsychiatric disorders that also have male preponderance (Hynd *et al.*, 1993; Peterson *et al.*, 1993; Castellanos *et al.*, 1994; Giedd *et al.*, 1994). Thus, sexually dimorphic brain maturational changes may interact with other unknown pathological influences, providing the striking sex differences seen in most pediatric behavioral disorders.

It is unclear from our data to what degree ventricular enlargement is at the expense of surrounding tissue. Nevertheless, in light of the frequent interpretation of increased ventricle:brain ratio as a general measure of cerebral damage it is noteworthy that such an increase is an integral part of normal pediatric development. It is also of note that the use of this ratio does not decrease the variability when compared to the variability in lateral ventricular volume alone.

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Asymmetries of both the caudate and putamen are small in degree (3.2% for the caudate and 13.0% for the putamen), but highly consistent, occurring in the dominant direction in 85% of the subjects for both structures. The right-greater-than-left caudate volume is in keeping with several studies of normal adults using large samples (Breier *et al.*, 1992, Flaum *et al.*, 1995). With growing awareness of more complex cognitive and motor functions of the basal ganglia (Graybiel *et al.*, 1994), further evidence of develop- mental complexity in man is of considerable interest. We will be examining asymmetries in relation to motor and cognitive development in future analyses.

The methodological limitations of cross-sectional study designs for developmental studies should be noted. Longitudinal studies, encouraged by findings of high rescan reliability for quantification of brain structure sizes (Giedd *et al.*, 1995a), are currently underway. The enormous variability of brain structure sizes noted in this population, and the heterochronous nature of most developmental curves, necessitates large samples to characterize neuroanatomic changes in human brain development. Correction for height, weight or total brain size only partially reduces the variability. The relative merits of using actual sizes or sizes corrected for total brain volume are a source of considerable debate (Arndt *et al.*, 1991), although both approaches have potential utility in elucidating form/function relationships in the brain.

The quantification of natural, gender-specific variability and covariability provided by our study is in itself a useful tool in on-going efforts to identify and to characterize greater than expected inter- and intrasubject deviations in brain structure sizes. The robust maturational effects detectable across this clinically relevant age range will be important comparison measures in studies of neurodevelopmentally impaired children. For example, in males with ADHD, age-related decreases in caudate volume were not observed and increases in ventricular enlargement were significantly diminished (Castellanos *et al.*, 1996).

It is anticipated that the interaction of gender effects and specific disease processes will be a major contribution of this large normative study in our ongoing comparative studies of pediatric neuropsychiatric disorders.

Notes

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